REMARKS

Claims 77-96 have been canceled without prejudice or disclaimer. Claims 97-112 have been added and therefore are pending in the present application. Claims 97-112 are supported by claims 77-96.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Rejection of Claims 77-96 under 35 U.S.C. 112

Claims 77-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Office stated:

> The description of the methods recited by the claims is aberrant because the specification actually exemplifies and describes methods of screening, or selection, or identification, among multiple, variegated polypeptide products ... to evaluate the immunogenicity of the variegated products wherein proposed or actual epitopes in the amino acid sequence of the reference protein are altered and an animal's immune response to the variegated polypeptides is assessed, whereby one or more variegated polypeptide products are identified as providing reduced immunogenicity in an animal. Yet both of claims 77 and 87 contrarily describe methods 'for producing a DNA molecule encoding a [less immunogenic] variant of a reference protein", methods which culminate ... in 'forming a DNA molecule encoding the amino acid sequence of a selected variant.' These ultimate steps follow ... the initial preparation of multiple DNA molecules encoding multiple variants of a reference protein – because the specification does not disclose or suggest any other way of preparing a multitude of multiple variants. – thus the final process described by the claims is, in reality, an early, if not initial, process of methods the specification actually discloses.

Claims 77-96 have been rewritten as claims 97-112 to address this rejection. Applicants therefore submit that this rejection has been overcome.

II. The Rejection of Claims 77-96 under 35 U.S.C. 112

Claims 77-96 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Specifically, the Office stated that "Claims 77 and 87 ... are indefinite in the circuitous description they provide of the recapitulation of a process step as a terminal step in a process where the

process step must have already occurred early in a method, or at the outset of a method, for achi ving a certain, useful result."

Claims 77-96 have been rewritten as claims 97-112 to address this rejection. Applicants therefore submit that rejection has been overcome.

III. The Rejection of Claims 77-79, 85-90, 95 and 96 under 35 U.S.C. 103

Claims 77-79, 85-90, 95 and 96 are rejected under 35 U.S.C. 103 as being unpatentable over Ladner et al. (U.S. Patent No. 5,223,409). This rejection is respectfully traversed.

A. Ladner et al. Do Not Disclose or Suggest Mapping An Epitope, as Required By Applicants' Methods

Ladner et al. disclose a method of producing phage libraries of variants by controlled random mutagenesis ("variegation") and then selecting phages bearing those variants that do not bind to a target. The Ladner et al. method involves controlling the variegation to target amino acid residues located on the surface of streptokinase and raising an antibody against streptokinase for attachment to a column. The variants are selected by being placed in the antibody column and phages bearing those variants that do not bind to the column are collected and cultured.

However, Ladner et al. never map an epitope, i.e., Ladner et al. never identify the amino acids that form an epitope. Instead, Ladner et al. select variants that do not bind to the antibody column or which bind weakly when eluted in a salt gradient. Although some of these variants may have a mutation of an amino acid that forms an epitope, Ladner et al. do not disclose or suggest which mutations belong to an epitope or which mutations belong to the same epitope. For example, a variant selected by the method of Ladner et al. might contain five amino acid substitutions, three of which are part of epitopes, and two of which are due to the randomness of the variegated library design. Ladner et al. do not suggest any method of determining which of the five mutations are mutations of an epitope and which are not. Furthermore, Ladner et al. do not suggest any method of determining whether the three mutations that are mutations of an epitope are mutations of the same or different epitope.

Moreover, Ladner et al. state that, "Destroying binding frequently requires only that a single amino acid in the binding interface be changed." This indicates that Ladner et al. are not interested in mapping any epitope.

For the foregoing reasons, Ladner et al. do not map one or more epitopes of a reference protein.

At page 5, lines 17, 18 of the Office Action, the Office states that Ladner et al. "disclose many examples of practicing each step of the method taught in section 'V.R.'" This is respectfully traversed.

As mentioned in the previous response, the general objective of and all the working examples of Ladner et al. are directed to selecting variants that have increased binding to a target. Only in section 'V.R.' does the Ladner et al. reference (from column 102, line 44 – column 103, line 30) aim to select variants that do not bind to the target or bind less strongly to the target. This section is not supported by any working examples. As indicated in the previous response, the difference between selecting for increased binding and decreased binding is fundamental in nature because selecting for decreased binding will inherently be a selection for all the members of the phage library, which contain misfolded, inactivated, misprocessed, truncated, or otherwise dysfunctional variants of the target protein. Thus, the statement in Ladner et al. at column 103, lines 5-8, that "such mutants are tested to verify that the pharmacologically interesting properties have not been altered to an unacceptable degree by the mutations' would be understood by one of ordinary skill in the art to require an enormous testing program in order to identify functional variants. Thus, Ladner et al. do not disclose or suggest a method for mapping epitopes of a protein with a reasonable likelihood of success.

B. Ladner et al. Do Not Disclose or Suggest Raising Antibodies Against the Reference protein and Variants Thereof, as Required by the Method of Claim 97

In the Ladner et al. method, an antibody is raised against the reference protein and not against the reference protein and a variant thereof, as recited in claim 97. Thus, Ladner et al. do not teach or suggest the methods of claims 97-104.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. The Rejection of Claims 80-84 and 90-94 under 35 U.S.C. 103

Claims 80-84 and 90-94 are rejected under 35 U.S.C. 103 as being unpatentable over Ladner et al. (U.S. Patent No. 5,223,409) in view of either Zacharaiae et al. (Allergy, Vol. 36, pp. 513-516 (1981) or Arlian et al. (International Archives of Allergy and Applied Immunology, Vol. 91, pp. 278-284 (1990)). This rejection is respectfully traversed.

As provided in Section III, Ladner et al. do not teach or suggest the methods of the present invention. Applicants submit that Zachariae et al. and Arlian et al. fail to cure the deficiencies of Ladner et al.

Zachariae et al. disclose that exposure to detergent enzymes like Esperase® will cause IgE-mediated sensitization in persons.

Arlian et al. disclose that Alcalase and Savinase cause respiratory allergy. However, Arlian et al. is also silent with respect to teaching the method, as claimed herein.

However, neither Zachariae et al. nor Arlian et al. teach or suggest methods for selecting a variant of a reference protein, comprising mapping one or more epitopes of a reference protein and selecting a variant, which has an altered amino acid sequence of one or more epitopes of the reference protein and which evokes a lower immunogenic response in an animal than the reference protein.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 103. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

Date: January 16, 2004

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